

REMARKS/ARGUMENTS

Claims 104 and 123 have been amended to correct a clerical error which occurred with the earlier cancellation of claim 96. The amendments to claim 104 are not necessitated by any rejection or objection but rather are meant to conform it with dependent claim 123 and to encompass a preferred aspect of the invention.

Claim 109 has been amended to use alternate language to embrace the same subject matter without alterations in claim scope. Support for the change is found at least in claims 87 and 109 as previously presented.

Claim 110 has been amended to correct its dependency and to use language explicitly and implicitly present in claim 88.

No new matter has been introduced, and entry of the amendments is respectfully requested.

Applicants wish to express their thanks for the courtesy of an interview on October 14, 2003 between Applicants' representatives and Examiners Celine X. Qian and Ann Falk.

The interview focused on the rejection under 35 U.S.C. § 112, first paragraph, with Applicants' representatives presenting their view of the pending claims as sufficiently enabled in light of the evidence, including the declaration by Dr. S. Naylor. Examiner Qian maintained, however, her position, based on the allegation of a need to demonstrate enablement of delivering a therapeutic gene at the time of the invention.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 87-93, 101, 104, 109-116 and 120-125 were rejected under 35 U.S.C. § 112, first paragraph as allegedly enabled by the application as filed only with respect to delivery and expression of "a reporter or marker gene." Applicants have carefully reviewed the statement of the rejection as well as the previous assertions of this allegation during the prosecution of the instant application.

Applicants respectfully submit that with a thorough reconsideration of all the evidence in the instant application, including the information provided below, no *prima facie* case of non-enablement is possible and this rejection may be properly withdrawn. The requirement to review the evidence as a whole is set forth at MPEP 2164.05 and the cases cited therein.

As an initial matter, Applicants point out that the standard to be applied in establishing a *prima facie* case of non-enablement is set out in part at MPEP 2164.04, including *In re Marzocchi*<sup>1</sup> and the other cases cited therein. With reference to *Marzocchi*, the standard states in part that

“A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the *objective* truth of the statements contained therein which must be relied on for enabling support.” (underlining and italics added)

As the Examiner is no doubt aware, the above standard requires *objective* reasons to doubt the presumption of an enabling disclosure. Mere reliance on assertions of unpredictability are not enough. There must be objective reasons why undue experimentation is necessary to make and use the claimed invention.

Moreover, undue experimentation is not the same as the absence of experimentation. To the contrary, routine and repetitive experimentation, like that involved in the case of *In re Wands*<sup>2</sup>, is entirely contrary to an assertion of non-enablement.

In the instant application, the disclosure, and thus claims, were enabling as originally filed for the full scope of the claims because no adequate and objective reasons were presented to doubt the ability to express genes beyond reporter and marker genes. The instant

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<sup>1</sup> 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

rejection is allegedly based on the unpredictability “on how to achieve high and sustained level of expression of the therapeutic gene *in vivo*, hence achieve a therapeutic effect.” This basis for the rejection was maintained despite the fact that the instant application more than adequately demonstrates the ability to express sufficient levels of marker genes AND the fact that the specification describes multiple instances where the “therapeutic gene” is used to generate an active metabolite which kills the transduced phagocytes as well as nearby tumor cells by the “bystander effect” where non-transduced cells in the vicinity of transduced cells producing the active metabolite are also killed effectively. The allegation of a need for “high and sustained level of expression” is not an objective reason to doubt the ability to express enough of an enzyme, capable of producing a cytotoxic active metabolite, in the same manner as with the sufficient expression of marker genes in the working examples.

Despite the fact that the instant claims are enabled at the time of invention for the reasons provided above, Applicants submit herewith a second declaration<sup>3</sup> by Stuart Naylor, Ph.D. which provides additional discussion of how the instant application could be followed to adequately express a “therapeutic gene” under the control of a hypoxia response element (HRE) to result in tumor cell death *in vivo*. With respect to the emphasis on “enablement as of the filing date” under MPEP 2164.05(a) as asserted in the Office Action, and to the extent that the declaration reflects work that was performed after the filing date of the instant application, Applicants respectfully point out that MPEP 2164.05 expressly states that the requirement for an enabling requirement as filed “does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works.”

Here, the second Naylor declaration clearly demonstrates that contrary to the assertions by the Examiner, the claimed invention operates by using a tumor localized transduced phagocyte to express a “therapeutic gene” *in vivo* under the control of an HRE. More importantly, no more than routine experimentation, as opposed to the alleged need for undue experimentation, was used to arrive at the results described in the declaration.

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<sup>2</sup> 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

<sup>3</sup> The declaration has been provided in unexecuted form to expedite prosecution of the instant application. An executed version of the declaration will be provided as soon as it is available from Dr. Naylor.

Accordingly, Applicants respectfully submit that with a reconsideration of the instant rejection based on the weight of all the evidence presented, the instant rejection should be found to be misplaced such that it may be properly withdrawn. Early indication to that effect is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 89-93, 109, and 110 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for use of various language in the claims. Applicants respectfully traverse as follows.

Claims 89-93 were rejected based on the use of the phrase “wherein the mononuclear phagocyte further comprises a binding agent capable of binding to a cell surface element of the mononuclear phagocyte.” The Examiner’s position is that the claims are indefinite because it is “unclear where the binding agent is located.” (see Office Action on page 6). This rejection thus appears to be based on the view that because the binding agent can be placed at a variety of locations, then the location of the agent is “unclear”.

Applicants respectfully submit that mere breadth of a term or claim is not equivalent to indefiniteness. This is clearly set forth by the standards at MPEP 2173.04. Applying this standard to claims 89-93, there can be no *prima facie* case of indefiniteness merely because the location of the binding agent is not recited in the claims. The simple fact is that the claims broadly encompass the claimed invention where the binding agent is located at a variety of locations.

Additionally, Applicants respectfully submit that the claims are not indefinite when properly read in light of the content of specification. The specification sets forth information relating to binding agents and how they may be incorporated into mononuclear phagocytes. For example, such binding agents may be coupled to the mononuclear phagocytes of the invention, or complexed to the nucleotide constructs of the invention, or alternatively, may be internalized therein the mononuclear phagocytes of the invention by use of a viral vector. Examples of such use of binding agents are found throughout the specification, including at least pages 13-14. See also the Experimental section (pages 20-24) which shows examples of

retroviral vectors and adenoviral vectors which have been internalized in mononuclear phagocytes of the invention, non-viral vectors such as plasmid DNA constructs of the invention which have been complexed/compacted to mannosylated poly-L-lysine, and antibody or receptor conjugates made with the mononuclear phagocytes of the invention.

Accordingly, Applicants respectfully submit that this rejection is misplaced and may be properly withdrawn.

Claim 109 has been rejected with respect to the term “delivery system”. Claim 109 has been amended to use alternative language to embrace the same subject matter found in claim 109 as well as claim 87, from which claim 109 depends, without altering the scope of the claims. Accordingly, Applicants respectfully submit that this rejection may be properly withdrawn.

Claim 110 has been rejected as allegedly indefinite for use of terms for which antecedent basis is lacking in claim 87, from which claim 110 depends. Claim 110 has been amended above to correct a clerical error in its dependency and to recite language that is supported by claim 88. Accordingly, Applicants respectfully submit that this rejection may be properly withdrawn.

As such, Applicants believe that the alleged issues of indefiniteness have been addressed and that the rejections under 35 U.S.C. § 112, second paragraph may be withdrawn.

#### Claim Objections

Claim 123 was objected to as being dependent from a canceled base claim. As noted above, claim 123 has been amended to correct its dependency. Withdrawal of this objection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6151.

Respectfully submitted,



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